COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk discussion

Dr. Megan Wallace and Dr. Sara Oliver
ACIP Meeting
June 23, 2021
Current COVID-19 mRNA vaccine policy

- COVID-19 vaccines are recommended for persons 12 years of age and older in the United States under FDA’s Emergency Use Authorization
COVID-19 mRNA vaccines in adolescents and young adults

Risk after COVID-19 mRNA vaccines in adolescents and young adults
COVID-19 mRNA vaccines in adolescents and young adults

Risk after COVID-19 mRNA vaccines in adolescents and young adults

Benefits of COVID-19 mRNA vaccines in adolescents and young adults
COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk discussion

- Public health problem
  - COVID-19 infections and complications in adolescents and young adults
    - Epidemiology in adolescents and young adults 12–29 years of age
    - Post-COVID conditions, including MIS-C and MIS-A
    - Myocarditis

- Benefit/Risk assessment
  - Benefits of mRNA vaccines
  - Risk of myocarditis after mRNA vaccines

- Work Group interpretation

- Questions for ACIP
Public Health Problem
Overall COVID-19 cases in the US have been declining since January 22, 2020 – June 15, 2021.

[Graph showing the decline in COVID-19 cases in the US from January 22, 2020 to June 15, 2021.]

Overall COVID-19 cases in the US have been declining since January 22, 2020 – June 15, 2021.

https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases
Based on projections, cases may increase substantially in the setting of low vaccination rates and high variant transmissibility.
Variants of concern (VOC) are an increasing proportion of SARS-CoV-2 lineages circulating in the US

March 13 – June 19, 2021 with NOWCAST

<table>
<thead>
<tr>
<th>Collection Date, 2-weeks ending</th>
<th>Percent of Viral Lineages</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/27/21</td>
<td>B.1.526 29%</td>
</tr>
<tr>
<td>4/10/21</td>
<td>B.1.429 31%</td>
</tr>
<tr>
<td>4/24/21</td>
<td>B.1.526 41%</td>
</tr>
<tr>
<td>5/8/21</td>
<td>B.1.526 42%</td>
</tr>
<tr>
<td>5/22/21</td>
<td>B.1.526 40%</td>
</tr>
<tr>
<td>6/5/21</td>
<td>B.1.526 29%</td>
</tr>
<tr>
<td>6/19/21</td>
<td>B.1.526 31%</td>
</tr>
</tbody>
</table>

Variants of Concern

B.1.1.7 (Alpha) 52%

P.1 (Gamma) 16%

B.1.617.2 (Delta) 21%

B.1.351 (Beta) <1%

B.1.427/B.1.429 (Epsilon) <1%

CDC COVID Data Tracker As of 6/14/21; VOC=Variant of Concern; VOI=Variant of Interest
Adolescents and young adults have the highest COVID-19 incidence rates

COVID-19 Incidence Rate per 100,000 Population, by Age Group and Sex
April 1, 2021 – June 11, 2021

- 12-17 Years
- 18-24 Years
- 25-29 Years
- 30-49 Years
- 50-64 Years
- 65+ Years

COVID-19 Incidence Rate per 100,000 Population

https://covid.cdc.gov/covid-data-tracker/#demographics
Adolescents and young adults have the highest COVID-19 incidence rates

Since beginning of pandemic at least 7.7 million COVID-19 cases have been reported among persons aged 12–29 years
Adolescents and young adults are an increasing proportion of COVID-19 cases reported

As more older adults are vaccinated, adolescents & young adults make up greater % of total cases: 33% of cases reported in May 2021 among persons aged 12–29 years

https://covid.cdc.gov/covid-data-tracker/#demographicsovertime
COVID-19-associated hospitalization rates have remained stable in adolescents and young adults.

Weekly COVID-19-associated hospitalization rates, by age group
COVID-NET, March 7, 2020 – May 22, 2021

COVID-19-associated deaths continue to occur in adolescents and young adults

Since beginning of pandemic, 2,767 COVID-19 deaths have been reported among persons aged 12-29 years; 316 deaths reported since April 1, 2021

https://covid.cdc.gov/covid-data-tracker/#demographics
Post-COVID conditions can occur after COVID-19

- No standardized definition, but generally new or persisting symptoms from acute infection or exacerbation of a chronic condition ≥4 weeks after SARS-CoV-2 infection
- Reported after infections ranging from asymptomatic to severe
- Limited data in adolescents/young adults, but recent cross-sectional studies have shown evidence of new or persisting COVID symptoms in this age group\(^1,2\)
  - Up to one-half of study participants had symptoms 1 month post-diagnosis
  - Symptoms reported include fatigue, insomnia, rhinorrhea, muscle pain, headache, lack of concentration, exercise intolerance, dyspnea, chest pain

\(^1\)Buonsenso et al, Acta Paediatrica (2021)
\(^2\)Walsh-Messinger et al, medRXiv (2020)
Multisystem Inflammatory Syndrome in Children (MIS-C)

- Severe hyperinflammatory syndrome occurring 2–6 weeks after acute SARS-CoV-2 infection among persons <21 years old, resulting in a wide range of manifestations and complications
  - 60%–70% of patients are admitted to intensive care, 1%–2% die\(^1,2\)
- \textbf{4,018 MIS-C} cases have been reported to national surveillance as of June 2, 2021\(^3\)
  - Estimated incidence of 1 MIS-C case in 3,200 SARS-CoV-2 infections\(^4\)
  - 36% of cases in persons aged 12–20 years
  - 62% of reported cases have occurred in children who are Hispanic/Latino or Black, Non-Hispanic

Daily MIS-C cases and COVID-19 cases reported to CDC (7-day moving average)

https://www.cdc.gov/mis-c/cases/index.html; accessed 06/08/2021
Characteristics associated with Multisystem Inflammatory Syndrome in Adults (MIS-A)

- Single-center, retrospective cohort study identified 15 adults with MIS-A from those hospitalized with a positive SARS-CoV-2 test result\(^1\)
  - 15 (1.7\%) of 839 hospitalized patients
  - Patients with MIS-A were younger and more likely to have positive serologic test (SARS-CoV-2 antibodies) compared to acute COVID-19 patients.
    - Other demographic characteristics and comorbidities did not differ between MIS-A patients and patients with acute COVID-19
  - 8 of 15 MIS-A patients had cardiovascular involvement

- Case series of 27 MIS-A patients\(^2\)
  - Antibody testing required to identify SARS-CoV-2 infection in approximately one third of cases
  - Age range: 21 – 50 years
  - 26 (96\%) patients belonged to racial or ethnic minority groups
  - Three patients died

Epidemiology of myocarditis and pericarditis

- **Myocarditis** is inflammation of the heart muscle, and **pericarditis** is inflammation of the outer lining of the heart.

- Myocarditis and pericarditis generally occur more frequently in:
  - Young adults
  - Men
  - Persons with certain medical conditions or recent medical procedure

- Can occur after SARS-CoV-2 infection
  - Data to estimate frequency after COVID-19 is limited

- There is a spectrum of disease but for the purpose of the benefit-risk discussion we will refer to both myocarditis and pericarditis as myocarditis.

Gubernot D, Vaccine. [https://doi.org/10.1016/j.vaccine.2021.05.016](https://doi.org/10.1016/j.vaccine.2021.05.016) [https://www.nhlbi.nih.gov/health-topics/heart-inflammation](https://www.nhlbi.nih.gov/health-topics/heart-inflammation)
Myocarditis and COVID-19

- 1597 young athletes with recent SARS-CoV-2 infection had cardiac MRI\(^1\)
  - 37 (2.3%) with abnormal MRI findings
  - However, 24 (65%) of 37 had normal lab findings and no symptoms
  - Another study suggested some MRI findings may be related to remodeling from athletic training\(^2\)

- Retrospective study — children with acute myocarditis treated at a single center from 2018–2020\(^3\)
  - 27 children <18 years of age identified
  - 7/27 (26%) had evidence of prior SAR-CoV-2 infection or exposure
    - 6 ultimately diagnosed with MIS-C
  - Individuals with myocarditis/MIS-C related to SARS-CoV-2 had better clinical course
    - None diagnosed with acute fulminant myocarditis
    - Shorter duration of inotropic drug support and ICU stay
    - Did not require mechanical respiratory support

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\(^2\)Clark DE, et al. Circulation; 2021:143(6);  
\(^3\)Vukomanovic et al. *PIDJ*; 2021:40(5):e173–e178
Myocarditis after mRNA vaccines: Summary of clinical features

- Most commonly in males <30 years of age
- Symptom onset clusters in the week following vaccination
- Early data of acute outcomes have been good
  - Many cases hospitalized, usually for short duration
- No long-term data available yet
  - Continued monitoring ongoing

Summary

- COVID-19 incidence, hospitalization, and mortality rates are decreasing overall
  - Variants continue to spread and scenarios exist in which cases increase in fall
  - Adolescents are growing proportion of cases given vaccine coverage among adults

- Post COVID-19 conditions also impact adolescents and young adults
  - 4,018 MIS-C cases have been reported to national surveillance

- Myocarditis is a disease marked by inflammation of the heart muscle
  - Risk factors include younger age and male sex
  - Can occur with SARS-CoV-2 infection

- Myocarditis after mRNA vaccines noted with highest frequency in males aged 12–29 years following 2nd dose
  - Early outcomes have been encouraging, but no long-term data available yet
Benefits and Harms
COVID-19 mRNA vaccines in adolescents and young adults

Benefit and Risk Summary

Benefits
Estimated COVID-19 cases and hospitalizations prevented by mRNA COVID-19 vaccines, by age and gender

Potential harms
Estimated cases of myocarditis after mRNA COVID-19 vaccines, by age and gender
Clinical trial data demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19 among individuals ≥16 years of age
– Overall efficacy was 95% (95% CI: 90.3%, 97.6%)

Vaccine efficacy against COVID-19 associated hospitalization was 100%
(95% CI: -9.9%, 100%)

Also demonstrated high efficacy against symptomatic, laboratory-confirmed COVID-19 in adolescents aged 12–15 years
– Overall efficacy was 100%, immunogenicity non-inferior to 16–25 year old population
Benefits of the Moderna COVID-19 vaccine

- Clinical trial data demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19 among individuals ≥18 years of age
  - Overall efficacy was 94.1% (95% CI: 89.3%, 96.8%)

- Vaccine efficacy against COVID-19 associated hospitalization was 89% (95% CI: 13%, 99%)

Real-world effectiveness of mRNA COVID-19 vaccines

- Multiple real-world effectiveness studies from the United States and other countries demonstrate that a two-dose mRNA COVID-19 vaccination series in age groups for which the vaccine is recommended is effective
  - Against SARS-CoV-2 infection: 64–99% estimate range
  - Against COVID-19-associated hospitalization: 87–97% estimate range

Potential harms of the mRNA COVID-19 vaccines: After dose 2

- 133 million vaccine 2nd doses administered* and 636 reported myocarditis cases as of June 11, 2021
  - Additional potential myocarditis cases under review

<table>
<thead>
<tr>
<th>Age group</th>
<th>Females Cases$</th>
<th>Doses admin</th>
<th>Reporting rate†</th>
<th>Males Cases$</th>
<th>Doses admin</th>
<th>Reporting rate†</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-17 years old</td>
<td>19</td>
<td>2,189,726</td>
<td>8.68</td>
<td>128</td>
<td>2,039,871</td>
<td>62.75</td>
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<tr>
<td>18-24 years old</td>
<td>23</td>
<td>5,237,262</td>
<td>4.39</td>
<td>219</td>
<td>4,337,287</td>
<td>50.49</td>
</tr>
<tr>
<td>25-29 years old</td>
<td>7</td>
<td>4,151,975</td>
<td>1.69</td>
<td>59</td>
<td>3,625,574</td>
<td>16.27</td>
</tr>
<tr>
<td>30-39 years old</td>
<td>11</td>
<td>9,356,296</td>
<td>1.18</td>
<td>61</td>
<td>8,311,301</td>
<td>7.34</td>
</tr>
<tr>
<td>40-49 years old</td>
<td>18</td>
<td>9,927,773</td>
<td>1.81</td>
<td>34</td>
<td>8,577,766</td>
<td>3.96</td>
</tr>
<tr>
<td>50-64 years old</td>
<td>18</td>
<td>18,696,450</td>
<td>0.96</td>
<td>18</td>
<td>16,255,927</td>
<td>1.11</td>
</tr>
<tr>
<td>65+ years old</td>
<td>10</td>
<td>21,708,975</td>
<td>0.46</td>
<td>11</td>
<td>18,041,547</td>
<td>0.61</td>
</tr>
</tbody>
</table>

$ Cases reported through VAERS using a 7-day risk window
* Source of doses administered: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](https://covid.cdc.gov/covid-data-tracker/#vaccinations); Some age- and sex-specific doses administered data were imputed
† Reporting rate = myocarditis cases per 1 million mRNA COVID-19 vaccine doses administered
Summary of benefit-risk analyses

### Individual Level Benefit-Risk Analysis

- Evaluate direct benefits and risk, per million mRNA COVID-19 vaccine doses
- Examine sex and age differences in risk and benefits
- Calculations based on:
  - Recent COVID-19 case and hospitalization incidence
  - mRNA vaccine efficacy
  - mRNA vaccinations to date
  - Number of persons already vaccinated
  - Myocarditis risk within 7 days after dose 2
  - 120-day risk period

### Population Level Considerations

- Describe benefits of vaccination at population level
Benefits and risks after dose 2, by age group

For every **million** doses of mRNA vaccine given with current US exposure risk\(^1\)

COVID-19-Associated Hospitalizations Prevented

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Hospitalizations Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 – 17</td>
<td>3145</td>
</tr>
<tr>
<td>18 – 24</td>
<td>9027</td>
</tr>
<tr>
<td>25 – 29</td>
<td>12 – 17</td>
</tr>
<tr>
<td>30 – 39</td>
<td>18 – 24</td>
</tr>
<tr>
<td>40 – 49</td>
<td>50 – 64</td>
</tr>
<tr>
<td>65+</td>
<td>9027</td>
</tr>
</tbody>
</table>

Cases of Myocarditis

1 Based on hospitalization rates from COVID-NET as of May 22\(^{nd}\). Benefit/Risk calculated over 120 days.
Benefits and risks after dose 2, by age group

For every **million** doses of mRNA vaccine given with current US exposure risk$^1$

![Chart showing COVID-19-Associated Hospitalizations Prevented and Cases of Myocarditis by age group.]

1 Based on hospitalization rates from COVID-NET as of May 22$^{nd}$. Benefit/Risk calculated over 120 days.
Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

**Females 12–17 Years**
- **8,500** COVID-19 cases prevented
- **183** hospitalizations prevented
- **38** ICU admissions prevented
- **1** death prevented
- **8–10** myocarditis cases

**Males 12–17 Years**
- **5,700** COVID-19 cases prevented
- **215** hospitalizations prevented
- **71** ICU admissions prevented
- **2** deaths prevented
- **56–69** myocarditis cases

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.
Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

<table>
<thead>
<tr>
<th>Females 18–24 Years</th>
<th>Males 18–24 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>14,000 COVID-19 cases prevented</td>
<td>12,000 COVID-19 cases prevented</td>
</tr>
<tr>
<td>1,127 hospitalizations prevented</td>
<td>530 hospitalizations prevented</td>
</tr>
<tr>
<td>93 ICU admissions prevented</td>
<td>127 ICU admissions prevented</td>
</tr>
<tr>
<td>13 deaths prevented</td>
<td>3 deaths prevented</td>
</tr>
<tr>
<td>4–5 myocarditis cases</td>
<td>45–56 myocarditis cases</td>
</tr>
</tbody>
</table>

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.
Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

**Females 24–29 Years**

- 15,000 COVID-19 cases prevented
- 1,459 hospitalizations prevented
- 87 ICU admissions prevented
- 4 deaths prevented
- 2 myocarditis cases

**Males 24–29 Years**

- 15,000 COVID-19 cases prevented
- 936 hospitalizations prevented
- 215 ICU admissions prevented
- 13 deaths prevented
- 15–18 myocarditis cases

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.
Additional considerations for direct benefit and risk

Males 12–17 Years

5,700 COVID-19 cases prevented
215 hospitalizations prevented
71 ICU admissions prevented
2 deaths prevented
56–69 myocarditis cases

Additional benefits to prevent post-COVID conditions

Prevention of MIS-C
Prevention of prolonged symptoms
Protection against variants
Benefit-risk analyses

Population Level Considerations

- No alternatives to mRNA vaccines for the foreseeable future in adolescents
- Vaccination of students offers an added layer of protection against COVID-19 and can be an important tool to return to ‘normal’
- Higher levels of vaccination coverage can lead to less community transmission, which can protect against development and circulation of emerging variants
- Racial and ethnic minority groups have higher rates of COVID-19 and severe disease.1
  - Potential changes in vaccine policy, or anything that would impact vaccination coverage for adolescents/young adults may disproportionately impact those groups with highest rates of poor COVID-19 outcomes

Benefit-risk interpretations and limitations

- Direct benefit-risk assessment shows **positive balance** for all age and sex groups
  - Considers individual benefits of vaccination vs. individual risks
  - Benefits are likely an underestimate
    - Analysis was performed using reported rates of cases and hospitalizations
    - Likely represent only a fraction of the true cases that have occurred in the population
  - Still uncertainty in rates of myocarditis after mRNA vaccines
    - Not all cases are verified and crude rates were used

- Balance of risks and benefits **varies** by age and sex
  - Balance could change with increasing or decreasing incidence

- Limited data currently on risk of myocarditis in 12–15 year old population
  - Due to timing of recommendations, limited number of 2nd doses given
Clinical Considerations
# Vaccine considerations in people with a history of myocarditis or pericarditis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericarditis prior to COVID-19 vaccination</td>
<td>Receive any FDA-authorized COVID-19 vaccine</td>
</tr>
<tr>
<td>Pericarditis after 1\textsuperscript{st} dose of an mRNA COVID-19 vaccine but prior to 2\textsuperscript{nd} dose</td>
<td>Proceed with a 2\textsuperscript{nd} dose of mRNA COVID-19 vaccine after resolution of symptoms. Discuss with patient, guardian, and clinical team</td>
</tr>
<tr>
<td>Myocarditis prior to COVID-19 vaccination</td>
<td>Receive any FDA-authorized COVID-19 vaccine if heart has recovered</td>
</tr>
<tr>
<td>Myocarditis after 1\textsuperscript{st} dose of an mRNA COVID-19 vaccine but prior to 2\textsuperscript{nd} dose</td>
<td>Defer 2\textsuperscript{nd} dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2\textsuperscript{nd} dose under certain circumstances. Discuss with patient, guardian, and clinical team</td>
</tr>
</tbody>
</table>
Work Group Interpretation
COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk discussion

Work Group Interpretation

- Initial presentations are reassuring; however, continued monitoring of cases, clinical course, and long-term outcomes of myocarditis after mRNA vaccines will be important.

- Need to follow the benefit-risk balance as we learn more around myocarditis, as well as updates to epidemiology (cases, variants, etc).

- Currently, the benefits still clearly outweigh the risks for COVID-19 vaccination in adolescents and young adults.
COVID-19 mRNA vaccines in adolescents and young adults

Current COVID-19 vaccine policy

- COVID-19 vaccines are recommended for persons 12 years of age and older in the United States under FDA’s Emergency Use Authorization
Questions for ACIP

1. What does ACIP think about the benefit-risk balance of COVID-19 vaccines in adolescents and young adults, in the setting of reports of myocarditis?

2. What additional information or analyses could inform these discussions as we continue to closely monitor this situation?
Acknowledgements

- Stephen Hadler
- Gayle Langley
- Julia Gargano
- Jessica MacNeil
- Heather Scobie
- Danielle Moulia
- Mary Chamberland
- Nicole Reisman
- Jack Gersten
- Eddie Shanley
- Hannah Rosenblum

- COVID-19 Vaccine Task Force
- Vaccine Safety Team
- Immunization team
- Epi Task Force
  - MIS-C unit
  - COVID-NET
- Data, Analytics and Visualization Task Force
- Division of Healthcare Quality Promotion
- Respiratory Viruses Branch